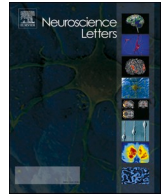




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



# Neurological issues during COVID-19: An overview

Avindra Nath <sup>\*</sup>, Bryan Smith

Section of Infections of the Nervous System, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, United States

## ARTICLE INFO

### Keywords:

Coronavirus  
Brain  
Neurological  
Infections  
Virus

## ABSTRACT

COVID-19 has shaken the core of the medical health system. The wide spread death and destruction of patients and health care workers in unprecedented in the modern era. While the pulmonary complications have received the most attention, it is the neurological manifestations that are disabling, persistent and common in patients infected with SARS-CoV-2. The entire neuro-axis can be involved resulting in a wide variety of manifestations. While the pathophysiology is not well understood, many of the clinical manifestations seem to be immune mediated. The socio-economic consequences of these complications are dire. These unprecedented times also calls for unprecedented action. Novel clinical trial designs need to be considered so that multiple agents can be studied. In the context of these clinical trials, disease pathophysiology and standardized batteries and biological markers for patient assessment need to be developed.

## 1. Introduction

In COVID-19, we face the biggest challenge in modern times. History teaches us that many of the pandemics have each, killed more people on this planet than all the wars combined. For example, in the 1300's the plague is said to have killed 25 million people in Europe. In the 1600's small pox killed 20 million indigenous people in North America. The influenza epidemic of 1918–19 killed about 30–50 million people. Similar proportions of people have been killed by polio, yellow fever, measles and HIV infection. Unfortunately, SARS-CoV-2 belongs to this category. In a matter of a few months SARS-CoV-2 has rapidly spread to every corner of the world and no country has been spared. The number of infections and deaths continue to rise at an exponential rate. As of November 1, 2020, there are nearly 100,000 new infections per day in United States and nearly a quarter million people have already died in the country [1]. What about the people who survive the infection? Nearly 10–35 % of survivors complain of disabling and persistent neurological symptoms [2]. With nearly 50 million people already infected world-wide [1], the socioeconomic consequences are unfathomable. Even if we have an effective vaccine, millions of people will have long-term consequences. The burden of care will fall on the shoulders of neurologists and we need to be prepared to take care of them. Below is a summary of the major neurological manifestations of the infection.

The neurological manifestations can be broadly divided into two categories; those that occur during the acute phase of the infection and

the post-viral manifestations.

## 2. Parainfectious complications

While anosmia is the most common and an early manifestation of the infection, encephalopathy is the most common neurological manifestation in hospitalized patients.

### 2.1. Encephalopathy

Nearly one third of hospitalized patients with COVID-19 develop encephalopathic symptoms. These can range from alteration in consciousness to delirium and seizures in some. Patients with altered mental status are hospitalized for three times as long and two-thirds are unable to manage activities of daily living at the time of discharge [3]. Encephalopathy seems to be more common in adults. The underlying causes are complex. In individuals with significant pulmonary disease or multiorgan involvement, hypoxic or metabolic abnormalities may be major contributors to the encephalopathy. The brain may also be vulnerable to systemic immune abnormalities. Some patients may develop an acute necrotic hemorrhagic encephalopathy which is thought to be cytokine mediated [4,5]; others have intrathecal synthesis of antibody. A cytokine release syndrome in which patients develop confusion, tremor, cerebellar ataxia, behavioral alterations, aphasia, pyramidal syndrome, coma, cranial nerve palsy, dysautonomia, and central hypothyroidism has also been described. These patients respond

<sup>\*</sup> Corresponding author at: Bldg 10, Rm 7C-103, 10 Center Drive, Bethesda, MD 20892, United States.

E-mail address: [natha@ninds.nih.gov](mailto:natha@ninds.nih.gov) (A. Nath).

<https://doi.org/10.1016/j.neulet.2020.135533>

Received 2 November 2020; Received in revised form 16 November 2020; Accepted 22 November 2020

Available online 25 November 2020

0304-3940/Published by Elsevier B.V.

to corticosteroid therapy [6,7]. Some others may develop wide spread microcerebral hemorrhages [8].

The SARS-CoV-2 virus is not especially neurotropic. It is not a virus that has a stereotypical neurologic syndrome like polio or rabies, and from what we know, it has very limited invasion of any neural cells. The virus is rarely found in the brain and even so is in very low copy numbers [9]. Autopsy studies show impressive invasion by immune cells particularly macrophages and lymphocytes in perivascular regions and the parenchyma [9]. The pathology is particularly prominent in the olfactory system and the brainstem. While it is intriguing to consider that viral invasion may occur in these regions via trans-neuronal spread as has been shown in mouse models with other coronaviruses either via the olfactory system or the vagal nerve as it innervates the respiratory and gastrointestinal tracts [10], concrete evidence for such neuroinvasion by SARS-CoV-2 is lacking. In rare individuals the virus has been detected in the cerebrospinal fluid with signs of encephalitis with seizures [11].

Delirium for patients with COVID-19 has been especially common. Rarely it is present at onset and typically associated with sepsis, but it is otherwise seen in the critical care setting where causes are multifactorial. In one series 84 % of COVID-19 patients in the ICU had delirium with a combination of acute attention, awareness, and cognition disturbances [12]. Outside of a true encephalitis, delirium in the ICU may arise from medications including sedative-hypnotics, anticholinergics, and corticosteroids; from the prolonged course of many COVID-19 sufferers' needs for mechanical ventilation; and from isolation. This latter component is especially challenging for patients. As with any respiratory virus setting, both the physical barriers of personal protection equipment and the limited contact with the medical team can lead to prolonged periods of isolation in the ICU. And because of social distancing requirements and many hospitals' need to restrict visitors, critically ill COVID-19 patients are almost always isolated from loved ones as well. The combination of these factors have been especially challenging for patients and it is not uncommon to hear stories of post-ICU trauma and anxiety that arise and persist well past the critical phase of illness.

Anosmia, and ageusia are common early symptoms. Nearly 40–60 % of patients develop loss of smell and upon testing nearly 90 % have alteration of smell [13]. The loss of taste is thought to be secondary to the loss of smell but can lead to loss of appetite and weight loss. Many patients recover their sense of smell, others may develop parosmia or permanent anosmia. The virus thought to invade the sustentacular or the support cells in vicinity to the olfactory nerve endings in the nasal mucosa which express the SARS-CoV-2 receptor ACE2 [14]. This is associated with swelling in that region [15]. To date, there is no direct evidence of infection of the olfactory nerve.

Strokes occur in nearly 1–5 % of hospitalized patients with COVID-19 [16,17]. Patients often develop a hypercoagulable state with high D-dimer levels. If untreated, they may develop arterial or venous occlusions, which can occur in multiple blood vessels simultaneously [18, 19]. Patients with underlying risk factors for stroke are at greater risk. Hemorrhagic strokes can also occur. Some develop microhemorrhages likely due to invasion of the vascular endothelium by the virus [20]. Embolic strokes can occur due to cardiac involvement by the virus.

### 3. Post-viral complications

Following the acute phase and sometimes during the acute phase, a variety of immune mediated syndromes can occur which can affect the brain, spinal cord or peripheral nerves. Such syndromes have been described with other viral infections and it is unclear at present if the manifestations with SARS-CoV-2 are in any way different. Acute disseminated encephalomyelitis has been reported with multifocal inflammatory lesions in the brain, spinal cord and optic nerve [21]. Guillain-Barre syndrome can manifest although in some patients the axonal form and in others the Miller Fisher variant has been described [22–24]. These manifestations have the typical autoantibodies and respond to immunotherapies. In some patients underlying autoimmune

syndromes such as myasthenia gravis can be unmasked. Patients with polyradiculoneuritis and cranial neuritis have also been described [25]. Rare cases of acute Parkinsonism and a single case of Creutzfeldt Jacob syndrome has been reported [26]. It remains unknown if other neurodegenerative diseases can be precipitated by this infection.

### 3.1. Long-Haul COVID

Most concerning however are the long-term complications of the viral infection. Nearly 10–35 % patients continue to complain of persistent symptoms most of which are neurological in nature [2]. This compilation of symptoms has been termed, Long-Haul COVID or Long COVID. Often these symptoms can first manifest after the acute phase of the illness. The severity of the acute phase does not predict the development of this syndrome either. The manifestations are very similar to myalgic encephalomyelitis/chronic fatigue syndrome. These patients complain of extreme exercise intolerance, dysautonomia, sleep disturbances, pain syndromes, low grade fever, dizziness, dyspnea and cognitive difficulties. Autonomic dysfunction can include palpitations, or tachycardia upon mild exercise or standing, hypo- or hypertension, gastroparesis, constipation or loose stools and peripheral vasoconstriction. In one series of hospitalized patients, 55 % complained of fatigue and 34 % complained of memory loss post-discharge [27]. The true extent of this syndrome, including the prevalence and duration of illness, remain unknown, but are an important avenue of research that will help us understand a more complete nature of the infection including its lasting effects.

### 4. Future directions

We need to develop standardized patient reported outcomes for each of the neurological symptoms. We need to consider conducting clinical trials even when the pathophysiology is not fully understood. Understanding disease pathophysiology is critical but considering the urgency of the situation, it can be studied in the context of clinical trials. Platform studies allow for the investigation of several therapeutic agents simultaneously and adaptive clinical designs permit the use of smaller sample sizes compared to the traditional double blind placebo controlled studies. These challenging times require innovative and unconventional solutions. We need to put our hearts and minds together and fight the tsunami.

### 5. Table: causes of encephalopathy with COVID-19

Hypoxia due to acute respiratory distress syndrome
Metabolic abnormalities due to multiorgan failure
Cytokine release syndrome
Acute disseminated encephalomyelitis
Acute necrotic hemorrhagic encephalopathy
Cerebral microhemorrhages
Viral encephalitis

### Acknowledgements

Supported by NINDS division of intramural research at National Institutes of Health

### References

- [1] <https://coronavirus.jhu.edu/map.html>.
- [2] M.W. Tenforde, S.S. Kim, C.J. Lindsell, et al., Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network - United States, march-june 2020, *MMWR Morb. Mortal. Wkly. Rep.* (69) (2020) 993–998.
- [3] E.M. Liotta, A. Batra, J.R. Clark, et al., Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients, *Ann. Clin. Transl. Neurol.* 11 (2020) 2221–2230.

- [4] N. Poyiadji, G. Shahin, D. Noujaim, M. Stone, S. Patel, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features, *Radiology* (2020), 201187.
- [5] J. Virhammar, E. Kumlien, D. Fallmar, et al., Acute necrotizing encephalopathy with SARS-CoV-2 RNA confirmed in cerebrospinal fluid, *Neurology* 95 (2020) 445–449.
- [6] P. Perrin, N. Collongues, S. Baloglu, et al., Cytokine release syndrome-associated encephalopathy in patients with COVID-19, *Eur. J. Neurol.* 27 (2020), <https://doi.org/10.1111/ene.14491>. Online ahead of print. August 10.1111/ene.14491.
- [7] S. Farhadian, L.R. Glick, C.B.F. Vogels, et al., Acute encephalopathy with elevated CSF inflammatory markers as the initial presentation of COVID-19, *BMC Neurol.* 20 (2020) 248.
- [8] S. Agarwal, R. Jain, S. Dogra, et al., Cerebral microbleeds and leukoencephalopathy in critically ill patients with COVID-19, *Stroke* 51 (2020) 2649–2655.
- [9] J.L. Matschke, C. Hagel, et al., Neuropathology of patients with COVID-19 in Germany: a post-mortem case series, *Lancet* (2020), [https://doi.org/10.1016/S1474-4422\(20\)30308-2](https://doi.org/10.1016/S1474-4422(20)30308-2).
- [10] M. Dube, A. Le Coupanec, A.H.M. Wong, J.M. Rini, M. Desforages, P.J. Talbot, Axonal transport enables neuron-to-Neuron propagation of human coronavirus OC43, *J. Virol.* 92 (2018) e00404–18.
- [11] T. Moriguchi, N. Harii, J. Goto, et al., A first case of Meningitis/Encephalitis associated with SARS-Coronavirus-2, *Int. J. Infect. Dis.* 94 (2020) 55–58.
- [12] J. Helms, S. Kremer, H. Merdji, et al., Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients, *Crit Care* 24 (2020) 491.
- [13] D. Hornuss, B. Lange, N. Schroter, S. Rieg, W.V. Kern, D. Wagner, Anosmia in COVID-19 patients, *Clin. Microbiol. Infect.* 26 (2020) 1426–1427.
- [14] D.H. Brann, T. Tsukahara, C. Weinreb, et al., Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia, *Sci. Adv.* (2020), 6.
- [15] T. Laurendon, T. Radulesco, J. Mugnier, et al., Bilateral transient olfactory bulb edema during COVID-19-related anosmia, *Neurology* 95 (2020) 224–225.
- [16] I. Bach, P. Surathi, N. Montealegre, et al., Stroke in COVID-19: a single-centre initial experience in a hotspot of the pandemic, *Stroke Vasc. Neurol.* (2020).
- [17] N. Majmundar, A. Ducruet, T. Prakash, A. Nanda, P. Khandelwal, Incidence, pathophysiology, and impact of coronavirus disease 2019 (COVID-19) on acute ischemic stroke, *World Neurosurg.* (142) (2020) 523–525.
- [18] T.J. Oxley, J. Mocco, S. Majidi, et al., Large-vessel stroke as a presenting feature of Covid-19 in the young, *N. Engl. J. Med.* 382 (2020) e60.
- [19] D.A. Berlin, R.M. Gulick, F.J. Martinez, Severe Covid-19, *N. Engl. J. Med.* (2020).
- [20] Z. Varga, A.J. Flammer, P. Steiger, et al., Endothelial cell infection and endotheliitis in COVID-19, *Lancet* 395 (2020) 1417–1418.
- [21] G. Novi, T. Rossi, E. Pedemonte, et al., Acute disseminated encephalomyelitis after SARS-CoV-2 infection, *Neurol. Neuroimmunol. Neuroinflamm.* 7 (2020).
- [22] H. Zhao, D. Shen, H. Zhou, J. Liu, S. Chen, Guillain-Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol.* (2020).
- [23] C. Gutierrez-Ortiz, A. Mendez-Guerrero, S. Rodrigo-Rey, et al., Miller Fisher syndrome and polyneuritis cranialis in COVID-19, *Neurology* 95 (2020) e601–e5.
- [24] J.A. Reyes-Bueno, L. Garcia-Trujillo, P. Urbaneja, et al., Miller-Fisher syndrome after SARS-CoV-2 infection, *Eur. J. Neurol.* (2020).
- [25] M. Dinkin, V. Gao, J. Kahan, et al., COVID-19 presenting with ophthalmoparesis from cranial nerve palsy, *Neurology* 95 (2020) 221–223.
- [26] M.J. Young, M. O'Hare, M. Matello, J.D. Schmammann, Creutzfeldt-Jakob disease in a man with COVID-19: SARS-CoV-2-accelerated neurodegeneration? *Brain Behav. Immun.* 89 (2020) 601–603.
- [27] E. Garrigues, P. Janvier, Y. Kherabi, et al., Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19, *J. Infect.* (2020).